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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/827,024 | 04/19/2004 | K. Keith Kwok | 217538 | 2493 |

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| EXAMINER | |
|---|---|
| KRISHNAN, GANAPATHY | |
| ART UNIT | PAPER NUMBER |
| 1623 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 01/16/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/827,024 | KWOK ET AL. | |
| | Examiner | Art Unit | |
| | Ganapathy Krishnan | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/26/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Claim Objections*

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claim 16 has been renumbered claim 16.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 recites the term complicated. The metes and bounds of the said recitation is not clear and renders the claim indefinite.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 20, 29, 33 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Nail et al (J. Pharmaceutical Sciences 2002, 91(4), 1147-55; document AI in IDS of July 26, 2004).

Nail et al teach a lyophilized formulation of Tobramycin (page 1149, left column, second and third full paragraphs; limitations of claim 17). They also teach compositions that contain less than 1.1% t-butyl alcohol (see figure 4 at page 1152; limitations of claim 20). The lyophilized Tobramycin is dissolved in 2mL of distilled water (page 1149, second full paragraph; limitations of claim 29). Since their Tobramycin is shown to contain some t-butyl alcohol (as seen by figure 4 at page 1152) the formulation in water above constitutes tobramycin in a sterile liquid composition comprising t-butyl alcohol too (limitation of claim 33). This also constitutes a composition wherein the amount of t-butyl alcohol is 4.5% or less by volume (limitation of claim 35).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16, 18-19, 21-28, 30-32, 34 and 36-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nail et al (J. Pharmaceutical Sciences 2002, 91(4), 1147-55; document AI in IDS of July 26, 2004).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Nail et al, drawn to powdered Tobramycin, teach the preparation of freeze-dried Tobramycin (lyophilized) wherein Tobramycin in combination with t-butyl alcohol (abbreviated as TBA by Nail) was freeze dried under vacuum at –45°C for 6 hours. Nail also teaches primary drying at –20°C for 50 hours at 100 mtorr pressure followed by secondary drying at 25°C for ten hours at 100 mtorr (page 1148, right column, see section entitled freeze-drying). According to Nail the freeze dried Tobramycin shows phase separation and does not break apart, retain high levels of the alcohol and do not readily reconstitute (page 1151, left column first paragraph). From this teaching one of ordinary skill in the art would recognize that reducing the amount of t-

butyl alcohol is necessary in order to produce a powder that can reconstitute as fast as the single-phase system.

Nail et al teach a lyophilized formulation of Tobramycin (page 1149, left column, second and third full paragraphs). They also teach compositions that contain less than 1.1% t-butyl alcohol (see figure 4 at page 1152). The lyophilized Tobramycin is dissolved in 2mL of distilled water (page 1149, second full paragraph). Since their Tobramycin is shown to contain some t-butyl alcohol (as seen by figure 4 at page 1152) the formulation in water above constitutes tobramycin in a sterile liquid composition comprising t-butyl alcohol too. This also constitutes a composition wherein the amount of t-butyl alcohol is 4.5% or less by volume.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce a lyophilized formulation of Tobramycin via a method as instantly claimed and also make compositions as instantly claimed since the general process steps and conditions for the same is seen to be taught in the prior art.

One of ordinary skill in the art would be motivated to use a method as instantly claimed since it is seen from the teaching of Nail that removal of residual alcohol is critical. It is also well known in the art that application of vacuum reduces the boiling point of a liquid and facilitates the removal of a solvent without decomposition. Hence slow heating of the Tobramycin containing residual alcohol under vacuum will help remove most of the residual alcohol to produce a single phase Tobramycin that will reconstitute easily. One of ordinary skill in the art will also be motivated to make compositions with different amounts in sealed vials as instantly claimed since such sealed compositions would not absorb moisture and cake.

It is well within the purview of one of ordinary skill in the art to adjust the process parameters like pressure, temperature and rate of heating based on the teaching of nail inorder to get an optimal removal of the residual t-butyl alcohol.

Claims 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Igarashi (US 4,166,114) in combination with Lagace et al (J. of Liposome Research, 1999, 993), 301-312.

Igarashi teaches a method of treating bacterial infections in humans and animals, which include soft tissue infections and urinary tract infections among others via administration of a composition comprising Tobramycin (col. 9, lines 38-46). Igarashi suggests the desirability of lyophilized powders and also suggests preparations in vials in a separate container in unit dosage form for making injectable solutions just before use and also dosages (col. 9, lines 9-37 and lines 46-54). However, Igarashi does not exemplify the said treatment with examples suing lyophilized Tobramycin.

Lagace et al teach the efficacy of Tobramycin against several bacteria including P. aeruginosa, Strenotrophomonas maltophilia, Burkholderia cepacia, E. coli and S. aureus bacterial colonies (abstract; page 305-308-efficacy and killing curves).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use lyophilized Tobramycin and its compositions for the treatment of bacterial infections in a patient as instantly claimed since such is seen to be taught in the prior art.

One of ordinary skill in the art would be motivated to do so since Tobramycin is seen to bee efficacious against several bacteria and the use of the lyophilized powder also has the advantage of preserving it for a long period of time and make injectable compositions just before use, as taught by Igarashi.

***Conclusion***

Claims 1-44 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GK

4/5/07

Shaojia Jiang
Supervisory Patent Examiner
Art Unit 1623